BLA Clinical Review Memorandum

Application Type	Original Application
STN	125771
CBER Received Date	June 30, 2022
PDUFA Goal Date	February 28, 2023
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Megha Kaushal, MD
Review Completion Date / Stamped Date	February 21, 2023
Supervisory Concurrence	Tejashri Purohit-Sheth, MD
Applicant	Sanofi
Established Name	Efanesoctocog Alfa
(Proposed) Trade Name	Altuviiio
Pharmacologic Class	Recombinant human factor VIII-Fc-VWF-XTEN
Formulation(s), including Adjuvants, etc.	Intravenous Injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution
Dosing Regimen	For Routine Prophylaxis: 50IU/kg once weekly; For On-Demand treatment and control of bleeding episodes and Perioperative management: 50IU/kg
Indication(s) and Intended Population(s)	For use in adults and children with Hemophilia A for: Routine prophylaxis to reduce the frequency of bleeding episodes; On-Demand treatment and control of bleeding episodes; Perioperative management of bleeding.
Orphan Designated (Yes/No)	Yes

TABLE OF CONTENTS

GLOSSARY 1

1. EXECUTIVE SUMMARY 2

1.1 Demographic Information: Subgroup Demographics and Analysis Summary 3
1.2 Patient Experience Data 4

2. CLINICAL AND REGULATORY BACKGROUND 5

2.1 Disease or Health-Related Condition(s) Studied 5
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 5
2.3 Safety and Efficacy of Pharmacologically Related Products 6
2.4 Previous Human Experience With the Product (Including Foreign Experience) 6
2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission 7
2.6 Other Relevant Background Information 7

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES 7

3.1 Submission Quality and Completeness 7
3.2 Compliance With Good Clinical Practices and Submission Integrity 7
3.3 Financial Disclosures 8

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 9

4.1 Chemistry, Manufacturing, and Controls 9
4.2 Assay Validation 9
4.3 Nonclinical Pharmacology/Toxicology 9
4.4 Clinical Pharmacology 10
4.4.1 Mechanism of Action 10
4.4.2 Human Pharmacodynamics 10
4.4.3 Human Pharmacokinetics 10
4.5 Statistical 10
4.6 Pharmacovigilance 11

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW 11

5.1 Review Strategy 11
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review 11
5.3 Table of Studies/Clinical Trials 11
5.4 Consultations 12
5.4.1 Advisory Committee Meeting (if applicable) 12
5.4.2 External Consults/Collaborations 13
5.5 Literature Reviewed (if applicable) 13

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS 13

6.1 Trial #1 13
6.1.1 Objectives (Primary, Secondary, etc) 13
6.1.2 Design Overview 14
6.1.3 Population 15
6.1.4 Study Treatments or Agents Mandated by the Protocol 15
6.1.5 Directions for Use 15
6.1.6 Sites and Centers 15
6.1.7 Surveillance/Monitoring 15
6.1.8 Endpoints and Criteria for Study Success 15
6.1.9 Statistical Considerations & Statistical Analysis Plan 16
6.1.10 Study Population and Disposition 16

6.1.11 Efficacy Analyses 17
6.1.12 Safety Analyses 22
6.1.13 Study Summary and Conclusions 24
6.2 Trial #2 25
6.2.1 Objectives (Primary, Secondary, etc) 25
6.2.2 Design Overview 25
6.2.3 Population 25
6.2.4 Study Treatments or Agents Mandated by the Protocol 25
6.2.5 Directions for Use 25
6.2.6 Sites and Centers 25
6.2.7 Surveillance/Monitoring 26
6.2.8 Endpoints and Criteria for Study Success 26
6.2.9 Statistical Considerations and Statistical Analysis Plan 26
6.2.10 Study Population and Disposition 26
6.2.11 Efficacy Analyses 27
6.2.12 Safety Analyses 29
6.2.13 Study Summary and Conclusions 31

7. INTEGRATED OVERVIEW OF EFFICACY 31

7.1 Indication #1 31
7.1.1 Methods of Integration 31
7.1.2 Demographics and Baseline Characteristics 31
7.1.3 Subject Disposition 31
7.1.4 Analysis of Primary Endpoint(s) 31
7.1.5 Analysis of Secondary Endpoint(s) 31
7.1.6 Other Endpoints 32
7.1.7 Subpopulations 32
7.1.8 Persistence of Efficacy 32
7.1.9 Product-Product Interactions 32
7.1.10 Additional Efficacy Issues/Analyses 32
7.1.11 Efficacy Conclusions 32

8. INTEGRATED OVERVIEW OF SAFETY 32

8.1 Safety Assessment Methods 32
8.2 Safety Database 32
8.2.1 Studies/Clinical Trials Used to Evaluate Safety 32
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations 32
8.2.3 Categorization of Adverse Events 32
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials 32
8.4 Safety Results 33
8.4.1 Deaths 33
8.4.2 Nonfatal Serious Adverse Events 33
8.4.3 Study Dropouts/Discontinuations 33
8.4.4 Common Adverse Events 33
8.4.5 Clinical Test Results 33
8.4.6 Systemic Adverse Events 33
8.4.7 Local Reactogenicity 33
8.4.8 Adverse Events of Special Interest 33
8.5 Additional Safety Evaluations 33
8.5.1 Dose Dependency for Adverse Events 33
8.5.2 Time Dependency for Adverse Events 33
8.5.3 Product-Demographic Interactions 33
8.5.4 Product-Disease Interactions 33
8.5.5 Product-Product Interactions 34
8.5.6 Human Carcinogenicity 34
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound 34

8.5.8 Immunogenicity (Safety) 34
8.5.9 Person-to-Person Transmission, Shedding 34
8.6 Safety Conclusions 34

9. ADDITIONAL CLINICAL ISSUES 34

9.1 Special Populations 34
9.1.1 Human Reproduction and Pregnancy Data 34
9.1.2 Use During Lactation 34
9.1.3 Pediatric Use and PREA Considerations 34
9.1.4 Immunocompromised Patients 34
9.1.5 Geriatric Use 35
9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered 35

10. CONCLUSIONS 35

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS 35

11.1 Risk-Benefit Considerations 35
11.2 Risk-Benefit Summary and Assessment 37
11.3 Discussion of Regulatory Options 37
11.4 Recommendations on Regulatory Actions 37
11.5 Labeling Review and Recommendations 37
11.6 Recommendations on Postmarketing Actions 38

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GLOSSARY

ABR	annualized bleeding rate
ADA	antidrug antibody
AE	adverse event
AJBR	annualized joint bleeding rate
AsBR	annualized spontaneous bleeding rate
BDD	beta domain deleted
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BU	Bethesda unit
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COA	Clinical Outcome Assessment
ED	exposure day
FAS	full analysis set
FDA	U.S Food and Drug Administration
FVIII	coagulation factor VIII
HA	Hemophilia A
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HJHS	Hemophilia Joint Health Score
IND	Investigational New Drug
IQR	interquartile range
IU	International units
IV	intravenous
PK	pharmacokinetic
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PTP	previously treated patient
rFVIII	recombinant FVIII
SAE	serious adverse event
SD	standard deviation
VWF	von Willebrand Factor

1. EXECUTIVE SUMMARY

Bioverativ submitted BLA 125771 as an original biologics license application (BLA) for the recombinant coagulation factor VIII Fc-von Willebrand factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN, Efanesoctocog alfa) product, referred to as BIVV001 with the proposed trade name Altuviiio. BIVV001 is the first FVIII replacement product with a pharmacokinetic (PK) profile independent of VWF.

Clinical trials that provided the evidence for safety and efficacy of BIVV001 were conducted under investigational new drug (IND) application 17464. Data from the completed PK, adolescent and adult (Study EFC16293), pediatric (Study EFC16295), and long-term safety and efficacy (LTS 16294) studies were included for review. Study EFC16293 and Study EFC16295 were the primary studies intended to support the marketing approval of BIVV001 under this BLA submission. These studies were reviewed to evaluate the efficacy and safety of BIVV001 for the following target indications for use in adults and children with Hemophilia A (HA):

- Routine prophylaxis treatment to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

The safety and efficacy of BIVV001 were evaluated in a total of 226 previously treated subjects in the adult, adolescent (n=159), and pediatric (n=67) studies who received at least one dose of BIVV001.

Study EFC16293 was a multicenter, open-label study that evaluated the PK, safety, and efficacy of treatment with BIVV001 for prophylaxis and treatment of bleeds and surgeries in previously treated adults and adolescents (≥12 years of age) with severe HA (congenital FVIII deficiency).

The study was divided into two parts. Part A enrolled 133 subjects. These subjects were on a prophylaxis treatment regimen prior to the study and received BIVV001 weekly as a prophylaxis treatment for up to 52 weeks. Subjects who completed 26 weeks were efficacy evaluable (n=128) and for the primary endpoint of mean ABR, had a mean annualized bleeding rate (ABR) [(95% Confidence Interval (CI) for all bleeds of 1.11 (0.8, 1.5) and median (interquartile range [IQR]) ABR for all bleeds of 0 (0, 1.2). The mean ABR for treated bleeds was 0.7 (95% CI 0.5, 1.0) and the median was 0 (0, 1.0). For the key secondary endpoint, non-inferiority of the intra-subject comparison of ABR between BIVV001 weekly prophylaxis and historical prophylaxis, was demonstrated (estimated mean difference in ABR of -2.30 (95% CI, -3.49, -1.11). There were 71 subjects with 0 bleeds.

Part B enrolled 26 subjects. These subjects were on an on-demand regimen prior to the study. Subjects received BIVV001 on demand for the first 26 weeks and then weekly for another 26 weeks. The mean (95% CI) ABR for all bleeds during prophylaxis was 0.9 (0.4, 1.8), a decrease from 22.2 (19.4, 25.4) with on-demand therapy. The median (IQR) ABR for all bleeds was 0 (0, 1.9) compared with 21.1 (16.8, 27) observed with on-demand therapy.

Perioperative management was evaluated for 12 subjects (11 adults and 1 child) who required 13 major surgical procedures and were treated with BIVV001 for surgical

hemostasis. Treatment with BIVV001 provided good or excellent hemostatic control in all major surgeries.

Study EFC16295 is an ongoing multicenter, open-label study to evaluate the PK, safety, and efficacy of treatment with BIVV001 for prophylaxis and treatment of bleeds in previously treated pediatric subjects (<12 years of age) with severe HA.

This study is ongoing; however, interim analyses were provided for review in support of the pediatric indication, as agreed upon at the pre-BLA meeting. There were 67 subjects treated with BIVV001 <12 years of age. Subjects with an efficacy period of greater than 26 weeks included 23 subjects and had a mean ABR (95% CI) of 3.6 (1.6, 8.4) and median of ABR of 0 (0, 4.5) for all bleeds. The mean treated ABR was 0.54 (95% CI: 0.23, 1.26) and median of ABR (Q1, Q3) of 0 (0, 1.3) compared to a pre-BIVV001 administration baseline mean treated ABR (SD) of 1.7 (2.1) and median of 1.0 (0; 8).

Study LTS16294 was an extension study of the main study and results were comparable to the main study. This study is ongoing. The safety review was concerning for three thrombotic events that were possibly related to BIVV001.

This submission did not trigger Pediatric Research Equity Act (PREA) due to Orphan Drug Designation. There are no postmarketing commitments or requirements.

Conclusion and Recommendation

Based on the review of the submitted data, this application has provided substantial evidence of the safety and effectiveness of BIVV001 in adults and children with HA based on adequate and well-controlled studies for the three indications (on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes). Although there are limited data in pediatric subjects (<12 years) with perioperative management, hemostatic data in major bleeding and pediatric PK data were extrapolated to support a pediatric perioperative indication. The overall benefit-risk profile favors regular approval of BIVV001 for use in adults and children with Hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes; On-Demand treatment and control of bleeding episodes; and Perioperative management of bleeding.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographics and baseline characteristics are summarized in Table 1.

Table 1. Demographics and Baseline Characteristics

Patient Age	<6 years	6 to <12 years	12 to <18 years	>18 years
N	31	36	25	134
Male, n (%)	31 (100)	36 (100)	25 (100)	133 (99.3)
Race, n (%)				
Not reported	0	4 (11.1)	8 (32)	18 (13.4)
White	25 (80.6)	25 (69.4)	11 (44)	86 (64.2)
Black	0	2 (5.6)	2 (8)	1 (0.7)
Asian	4 (12.9)	4 (11.1)	2 (8)	27 (20.1)
Other	2 (6.5)	1 (2.8)	2 (8)	1 (1.5)
Ethnicity, n (%)				
Hispanic/Latino	2 (6.5)	1 (2.8)	6 (24)	19 (14.2)

Patient Age	<6 years	6 to <12 years	12 to <18 years	>18 years
Age				
Mean (SD)	3.7 (1.3)	8.4 (2.1)	14.2 (1.6)	39.3 (13)
Median [Min, Max]	4 [1.4,5]	8 [6, 11]	14 [12, 17]	38 [18, 72]

Source: Adapted from BLA125771 and IR Amendment 28.
Abbreviations: SD, standard deviation.

Reviewer comment: *The limited sample size in Black and Hispanic subjects makes it challenging to reach conclusions about the efficacy of BIVV001 in these populations. Since the predilection for clinical bleeding is dependent on the degree of FVIII deficiency, race and ethnicity related differences in efficacy are expected to be minimal. Therefore, it is reasonable to extrapolate data from White/Asian subjects to the other races and ethnic groups.*

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒☐	Patient-reported outcome	6.1.11.5
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

HA is an X-linked congenital bleeding disorder caused by a deficiency of functional FVIII which manifests as bleeding episodes. It is the most common of the severe inherited coagulopathies with an incidence of approximately 1 in 10,000 births, with approximately 20,000 affected males in the United States. The relationship of bleeding severity correlates with clotting factor level. Patients with <0.01 IU/mL or <1% functional FVIII are categorized as having severe HA with spontaneous bleeding into joints or muscles. Moderate and mild cases of HA are characterized by clotting factor levels of 1% to 5% and 5% to <40%, respectively.

The severity of bleeding manifestations in hemophilia generally correlates with the degree of the clotting factor deficiency and can be acutely life threatening. Joint bleeding is the most frequent bleeding manifestation in children and adults. Repeated bleeding into the joints is debilitating and causes development of target joints from inflammation due to prior bleeding. To prevent joint destruction, the standard of care in patients with severe HA is primary prophylaxis with infusions of FVIII.

These regular infusions are initiated at the time of the first bleeding episode in a joint or earlier to prevent joint damage. However, inhibitory antibodies to infused FVIII products develop in a substantial percentage of patients treated with either plasma derived or recombinant FVIII products, making usual treatment with FVIII complicated. Prophylaxis has been shown to prevent complications later in life and to decrease the incidence of inhibitor formation.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there are over 10 licensed rFVIII products, some of which are full-length FVIII products and others that are beta domain deleted (BDD) products. These products are indicated for adults and children with HA for the control and prevention of bleeding episodes, and/or perioperative management, and/or routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage. The currently approved FVIII products are summarized in Table 2.

Table 2. Approved FVIII Products

Product	Category	Full Length or B Domain Deleted	Cell Expression	Year Approved
Recombinate	Recombinant	FL	CHO	1992
Kogenate	Recombinant	FL	BHK	1993
Refacto	Recombinant	BDD	CHO	2000
Advate	Recombinant Plasma/Albumin Free	FL	CHO	2003
Xyntha	Recombinant	BDD	CHO	2008
Novoeight	Recombinant	BDD	CHO	2013
Eloctate	Recombinant Fc Fusion Protein	BDD	HEK	2014
Obizur	Recombinant Porcine Sequence	BDD	BHK	2014

Product	Category	Full Length or B Domain Deleted	Cell Expression	Year Approved
Nuwiq	Recombinant	BDD	HEK	2015
Adynovate	Recombinant 20kDA PEGylated	FL	CHO	2015
Afstyla	Recombinant Single Chain	BDD	CHO	2016
Kovaltry	Recombinant	FL	BHK	2016
Jivi	Recombinant 60kDA PEGylated	BDD	BHK	2018
Esperoct	Recombinant 40kDA PEGylated	BDD	CHO	2019

Source: FDA review
Abbreviations: BDD, beta domain deleted; BHK, baby hamster kidney; CHO, Chinese hamster ovary; FL, full length; FVIII, coagulation factor VIII; HEK, human embryonic kidney.

2.3 Safety and Efficacy of Pharmacologically Related Products

Inhibitor formation and pathogen transmission are the main safety concerns when using FVIII replacement therapy to treat patients with HA. FVIII concentrates derived from human plasma first became available in the 1960s. The high risk of viral transmission from human plasma donors, underscored by the human immunodeficiency virus (HIV) epidemic in the 1980s, led to the development of recombinant FVIII (rFVIII) products that became available in the 1990s. The rFVIII products are genetically engineered and manufactured from animal cell lines, thus minimizing the risk of transmitting human pathogens. Full-length and modified rFVIII have been produced in Chinese hamster ovary or baby hamster kidney cells. In addition to the risk of pathogen transmission, the development of neutralizing antibodies, or inhibitors, has been and remains the most concerning safety issue following the administration of FVIII concentrates. The etiology of the development of inhibitors is thought to be a host immune response triggered by nonhuman proteins contained in the final rFVIII product. Purification steps in the manufacturing processes of successive generations of rFVIII aim to reduce both the transmission of pathogens and the development of inhibitors, which occurs in up to 30% of patients with severe Hemophilia A[1].

The development of inhibitors decreases the efficacy of replacement therapy, necessitates FVIII dosage increases and/or the use of “bypass” agents, increases the risk of unmanageable bleeding, and increases cost of treatment (by 3-5-fold)[2]. The incidence of inhibitor development is approximately 30% in severe disease and less in mild or moderate disease. The highest incidence is in previously untreated patients with severe disease (reported incidence from 3-52%). Incidence of inhibitor development in previously treated patients (PTPs) who have not previously developed an FVIII inhibitor is lower, reported as 0.9-4%. Potential risk factors for inhibitor development include genetic factors such as the type of FVIII gene mutation, human leukocyte antigen type, polymorphisms in immune regulatory regions, family history of inhibitors, and ethnic background; the immunologic environment during early treatment; and high intensity of treatment (either peak acute treatment or high overall treatment frequency).

2.4 Previous Human Experience With the Product (Including Foreign Experience)

At the time of the BLA submission, BIVV001 was not licensed in any other country.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

The U.S. Food and Drug Administration (FDA) had multiple interactions with the Applicant throughout the pre-IND, IND, and BLA processes. Key meetings and correspondence are detailed below:

- An End-of-Phase 2 meeting was conducted in 2019.
- In 2021, FDA granted Fast Track Designation. Clinical Outcome Assessment (COA) feedback was communicated in July of 2021.
- In April of 2022, a pre-BLA meeting was conducted where FDA agreed on a rolling submission to include interim analysis data for the pediatric population indication.
- In May 2022, Breakthrough Designation was granted.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure. It was adequately organized and integrated to conduct a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices and Submission Integrity

The Center for Biologics Evaluation and Research Bioresearch Monitoring (BIMO) branch issued inspection assignments for one domestic and three foreign clinical study sites participating in the conduct of protocol for Study EFC16293.

Please refer to the BIMO review memorandum for full details.

Four BIMO clinical investigator inspection assignments were issued in support of this BLA. The clinical study sites were selected based on subject enrollment, previous inspection history, and the data and information submitted in BLA 125771/0.

The inspections focused on the pivotal Study EFC16293 entitled, “A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients ≥12 Years of Age With Severe Hemophilia A.”

No significant objectionable inspectional findings were reported. Table 3 below summarizes the BIMO inspections:

Table 3. BIMO Inspection Sites

Site #	Study Site Name and Location	FDA Form 483 Issued?	Final Inspection Classification
139	Arbesú Hematology Institute Godoy Cruz, Argentina	No	NAI
283	Lille University Hospital Center Heart-Lungs Institute, Hemostasis and Transfusion Department Lille, France	No	NAI
122	Royal Prince Alfred Hospital Sydney, Australia	No	NAI
908	Michigan State University Center for Bleeding & Clotting Disorders East Lansing, Michigan, USA	No	NAI

Source: BIMO Review.
Abbreviations: BIMO, bioresearch monitoring; NAI, no action indicated.

3.3 Financial Disclosures

Complete financial disclosures were provided for the studies and reviewed. No significant financial interests or conflicts that could potentially bias the conduct of the study were identified. A complete list of clinical investigators and sub-investigators was provided and reviewed.

Covered clinical study (name and/or number): EFC16293
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 209
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Reviewer comment: *There were six investigators who received significant payments for general consulting, registration and speaker fees, travel, and accommodation. The details of the disclosable arrangements were provided. However, the Applicant did not specifically describe the steps taken to minimize potential bias. The majority of compensation to investigators was used for travel, consultations, and educational events. The clinical reviewer doesn't have any concerns regarding trial conduct or outcome as no specific concerns arose from review of site-specific data.*

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

BIVV001 is a fully recombinant fusion protein comprising a single-chain BDD analogue of human FVIII covalently fused to the Fc domain of human immunoglobulin G1, the FVIII-binding D'D3 domain of human VWF, and 2 XTEN polypeptides.

There were no significant issues related to chemistry, manufacturing, and controls (CMC) that were identified that would preclude approval. Please refer to the CMC memorandum for details.

4.2 Assay Validation

Required validation of applicable methods and their controls for FVIII assays have been completed and no issues were identified. FVIII plasma activity was measured by two different assays, the one-stage clotting assay, and chromogenic assay. The review primarily utilized he one-stage clotting assay as this was the most conservative of the assays.

4.3 Nonclinical Pharmacology/Toxicology

PK and toxicokinetic assessments were performed following single and repeat intravenous (IV) administrations of BIVV001 in hemophilia A (HA) mice, (b) (4) rats, and (b) (4) monkeys. Systemic exposure levels after a single administration of BIVV001 in mice, rats, and monkeys showed a dose-dependent proportional increase in maximum concentration and area under the concentration-time curve. The terminal half-life of BIVV001, which reflects the exposure and clearance of the fusion protein in plasma, was approximately 30 hours in mice and monkeys and approximately 20 hours in rats.

The no-observed-adverse-effect level was the maximum dose level administered, 750 IU/kg/dose, which is 15-fold higher than the maximum recommended prophylactic clinical dose level of BIVV001 (50 IU/kg once weekly). No significant issues were identified that raise safety concerns.

Please refer to the Pharmacology/Toxicology review for complete details.

4.4 Clinical Pharmacology

BIVV001 temporarily replaces the missing FVIII needed for effective hemostasis. BIVV001 has demonstrated 3- to 4-fold prolonged half-life relative to other standard and extended half-life FVIII products.

4.4.1 Mechanism of Action

BIVV001 is a rFVIII analogue fusion protein that is independent of endogenous VWF, thereby overcoming the half-life limit imposed by FVIII-VWF interactions. The D'D3 domain of VWF is the region that interacts with FVIII. Appending the D'D3 domain of VWF to a rFVIII-Fc fusion protein provides protection and stability to FVIII and prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII half-life imposed by VWF clearance.

The Fc region of human immunoglobulin G1 binds to the neonatal Fc receptor, part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by recycling them back into circulation, thus prolonging the plasma half-life of the fusion protein.

BIVV001 contains 2 XTEN polypeptides that alter the hydrodynamic radius of the fusion protein, thus reducing rates of clearance and degradation and improving PK properties. In BIVV001, the natural FVIII B domain (except 5 amino acids) is replaced with the first XTEN, inserted in between FVIII N745 and E1649 amino acid residues; the second XTEN is inserted in between the D'D3 domain and Fc.

4.4.2 Human Pharmacodynamics

Administration of BIVV001 increases plasma levels of FVIII, temporarily correcting the coagulation defect in patients with HA.

4.4.3 Human Pharmacokinetics

The PK parameters were based on plasma FVIII activity measured by the activated partial thromboplastin clotting time-based one-stage clotting assay. Weekly dosing of 50 IU/kg of BIVV001 showed minimal accumulation. With a once-weekly dose at 50 IU/kg, BIVV001 provided FVIII activity in the normal to near-normal range (>40 IU/dL) for three to four days and >10 IU/dL at the end of the weekly dosing interval in adults and adolescents. A once-weekly dose of BIVV001 at 50 IU/kg provided FVIII activity in the normal to near-normal range (>40 IU/dL) for 2 to 3 days, >10 IU/dL for approximately 6 to 7 days, and in the mild hemophilia range (>5 IU/dL) at the end of the weekly dosing interval in both cohorts of children <12 years of age.

Evaluation of the PK/PD data for BIVV001 supported the recommended dose of 50 IU/kg in both adults and children. Please refer to Clinical Pharmacology review memorandum for complete details.

4.5 Statistical

The statistical reviewer verified that the primary endpoint analyses and key secondary endpoints cited by the Applicant were supported by the submitted data in the adult and adolescent study. The statistical reviewer did not support the pediatric indication. Please see below for discussion in Section 6.2.13. Please refer to Biostatistics Review memorandum for details.

4.6 Pharmacovigilance

No postmarketing requirements or commitments will be planned post approval. The applicant plans a post approval voluntary study to assess safety of use of ALTUVIIIO in previously untreated patients (PUPs), and there is an ongoing long-term follow-up study of clinical trial participants. For 3 years following approval, the applicant will be required to conduct enhanced pharmacovigilance for thromboembolic events (TEEs), with expedited reporting of all TEEs (regardless of seriousness) and sponsor assessment for TEEs (based on cumulative and interval safety data) in periodic safety reports. Routine pharmacovigilance will be utilized for surveillance.

Please refer to Office of Biostatistics and Epidemiology memorandum for details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Clinical trials that provided the evidence for safety and efficacy of BIVV001 were conducted under IND 17464. Data from the completed adult and adolescent study (Study EFC16293) and interim results from the pediatric study (Study EFC16295) served as the primary basis for review. Data reviewed included the integrated summary of safety, summary of clinical safety, summary of clinical efficacy, individual clinical study reports, patient narratives, numerous information requests, and data in the public domain. An integrated summary of efficacy was not appropriate for the adult and pediatric studies due to different study designs and dosing regimens used in the trials. Analyses were performed using JMP 16 to reproduce key efficacy and safety analyses based on the submitted datasets and to conduct additional exploratory analysis.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Documents pertinent to this review were provided in BLA125771/0 and IND 17464, including the overview, analyses datasets, clinical summary, and clinical study reports.

5.3 Table of Studies/Clinical Trials

An overview of the clinical trials is presented in Table 4 below.

Table 4. Clinical Trials

Type of study	- Study identifier - Location of study report - Coordinating Investigator (and center) - Number of centers	- Objective(s) of study - Study design and type of control	Test product(s): - Formulation - Dosage regimen - Route of administration	Reference therapy: - Formulation - Dosage regimen - Route of administration	Number of study participants - Total[a, b] - Gender[a] (M/F) - Race[a] (C/B/O/A/NR) - Age[a] mean ± SD (range) - Treatment group[a]	Healthy study participants or diagnosis of study participants	Duration of treatment	Study status Type of report
Study reports of controlled clinical studies pertinent to the claimed indication								
Efficacy, safety and PK	[EFC16293]/ XTEND-1 Module 5.3.5.1 Dr A Von Drygalski, (Hemophilia and Thrombosis Treatment Center UCSD UC San Diego, USA) 51 active centers	- Primary: to evaluate the efficacy of BIVV001 as a prophylaxis treatment in adult and adolescent PTPs with severe hemophilia A, ≥12 years of age - A multinational, multicenter, open-label Phase 3 study.	BIVV001: - Lyophilized powder in a sterile vial that required reconstitution with sterile water for injection - 50 IU/kg once weekly for 52 weeks in Arm A - 50 IU/kg on demand for 26 weeks followed by a switch to 50 IU/kg once weekly for 26 weeks in Arm B - Intravenous injection	N/A	- 159/149 (Arm A: 133/124 Arm B: 26/25) - 158/1 - 97/3/4/29/26 - 35.4 ±15.1 (12-72) - Arm A: 133 ; Arm B: 26	Adult and adolescent PTPs with severe hemophilia A, ≥12 years of age	52 weeks	Complete Full
Other	[EFC16293 Clinical Outcome Assessment dossier] Module 5.3.5.1 - N/A - N/A	N/A	N/A	N/A	N/A	N/A	N/A	Complete Full
Study reports of Uncontrolled clinical studies								
Safety, efficacy and PK	[EFC16295]/ XTEND-Kids Module 5.3.5.2 Prof Karin Fijnvandraat University of Amsterdam, Amsterdam, The Netherlands 38 active centers	- Primary: to evaluate the safety of BIVV001 in previously treated pediatric patients <12 years of age with severe hemophilia A - A multinational, multicenter, open-label Phase 3 study	BIVV001: - Lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection - 50 IU/kg once weekly - intravenous injection	N/A	- 67/0 (31 participants <6 years of age and 36 participants 6 to <12 years of age) - 67/0 - 50/2/3/8/4 - 6.24 ±2.93 (1.4-11) - All participants were treated with BIVV001 once-weekly prophylaxis	Previously treated pediatric patients with severe hemophilia A	52 weeks	Ongoing Interim analysis CSR
Safety and efficacy	[LTS16294]/ XTEND-ed Module 5.3.5.2	- Primary: to evaluate the long-term safety of BIVV001 in previously treated patients with severe hemophilia A -A multinational, multicenter, open-label Phase 3 study	BIVV001: - Lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection - 50 IU/kg once weekly - Intravenous injection	N/A	- Arm A: 114/0; Arm B: 32/0; Arm C: 4/0 - Arm A: 113/1; Arm B: 32/0; Arm C: 4/0 - Arm A: 79/2/0/23/10; Arm B: 0/0/0/31/1; Arm C: 4/0/0/0/0 - Arm A: 36.8 ±15.3 (13-74); Arm B: 26.8 ±14.2 (12-67); Arm C: Not calculated - All participants were treated with BIVV001 once-weekly prophylaxis Data available as of data cut-off date, 24 Jan 2022, and presented in Module 5.3.5.3 Reports of Analyses of Data From More Than One Study [ISS Appendix 1] and [ISS Appendix 2]	Previously treated patients with severe hemophilia A, in 3 arms Arm A: participants who have completed Study EFC16293 or Study EFC16295, or Arm B or Arm C of Study LTS16294 Arm B: PTPs in China, newly initiated on BIVV001 Arm C: PTPs who are planned to undergo major surgery, newly initiated on BIVV001	Arm A: up to 4 years Arms B and C: 52 weeks	Ongoing Protocol

Source: Tabular Listing of Clinical Studies BLA 125771 Module 5.2.
Abbreviations: CSR, clinical study report; N/A, not applicable; PK, pharmacokinetics; PTP, previously treated patient; SD, standard deviation.

5.4 Consultations

The FDA COA consultants were requested by the clinical team during the review of this BLA to provide review support of Patient Reported Outcomes.

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was not convened because the biologic is not the first in its class. Additionally, the design of the clinical study is similar to studies conducted to

support other approved products and the review of the application did not raise significant safety or efficacy concerns that would warrant a public discussion and could not be addressed through information in the label. Consultative expertise was not required, and no public health concerns arose upon review of this file.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations that were requested by the clinical reviewer in the review of this BLA.

5.5 Literature Reviewed (if applicable)

1. Gouw SC, van den Berg HM, et al: Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. Blood. 121(20):4046-4055, 2013.
2. Calvez T, Chambost H, et al: Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. Blood. 124(23):3398-3408, 2014.
3. Collins PW, Palmer BP, et al: Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. Blood. 124(23):3389-3397, 2014.
4. Vezina C, Carcao M, et al: Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010. Haemophilia. 20(6):771-776, 2014.
5. Fisher K, Lassila, R, et al. Inhibitor development in haemophilia according to concentrate: four-year results from the European Haemophilia Safety Surveillance (EUHASS) project. Thromb Haemost. 113(5):968-975, 2015.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

Study EFC16293: This was a Phase 3, open-label, multinational, multicenter study of the safety, efficacy, and PK of IV BIVV001 in PTPs ≥12 years with severe HA (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe HA).

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to evaluate the efficacy of BIVV001 as a prophylaxis treatment with the primary endpoint of ABR.

Key secondary objectives and endpoints included:

- To evaluate the efficacy of BIVV001 as a prophylaxis treatment by
  - Intrapatient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the ABR with historical prophylaxis for subjects in Arm A
  - Intrapatient comparison of ABR during the once-weekly prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B
- To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes by

- Number of injections and dose of BIVV001 to treat a bleeding episode per study arm and treatment regimen
- To evaluate the efficacy for perioperative management
  - via Surgeon's assessment of response to BIVV001 per the International Society on Thrombosis and Hemostasis 4-point response scale and total BIVV001 consumption during perioperative period for major surgery
- To evaluate the safety and tolerability of BIVV001 treatment
- To evaluate PK

Exploratory endpoints included:

- To evaluate the effect of prophylaxis on joint health outcomes via Hemophilia Joint Health Score (HJHS)
- To evaluate quality of life outcomes
  - via the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) score from baseline and changes in Patient-Reported Outcomes Measurement Information System (PROMIS).

6.1.2 Design Overview

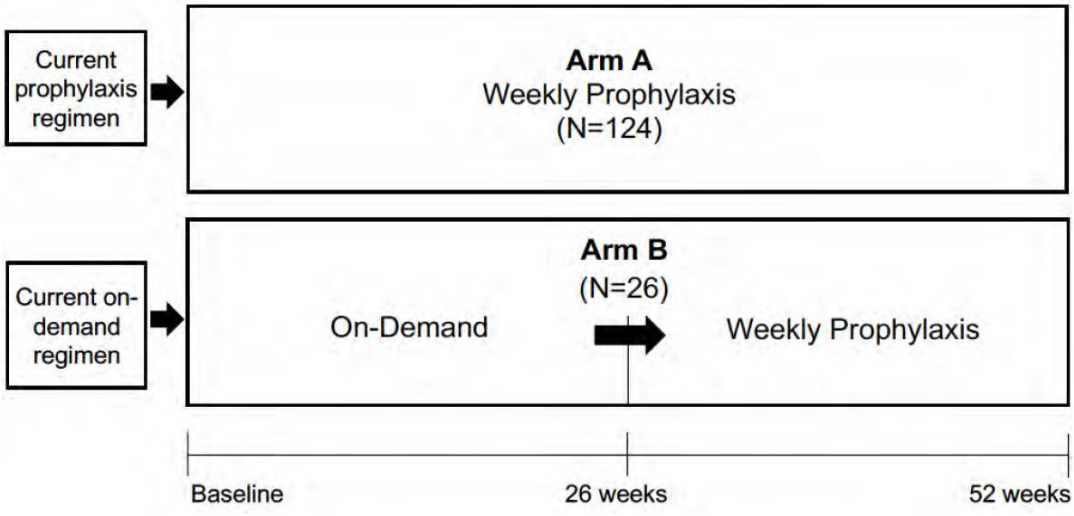
The study was comprised of two arms:

- Arm A: subjects who were on prophylaxis treatment with FVIII prior to the study and received BIVV001 at a dose of 50 IU/kg IV once weekly for up to 52 weeks.
- Arm B: subjects who received an on-demand regimen prior to the study and received IV BIVV001 at a dose of 50 IU/kg on demand for 26 weeks followed by the prophylaxis regimen at a dose of 50 IU/kg IV once weekly for another 26 weeks.

Subjects in either arm who underwent major surgery were included in the Surgery subgroup. All subjects were to receive a preoperative dose of BIVV001 at 50 IU/kg prior to the surgical procedure and the dose would be adjusted to maintain FVIII at 100%.

See the study design in Figure 1.

Figure 1. Study Design



Source: BLA 125771 clinical study report Figure 1 pg22/150.

6.1.3 Population

Subjects enrolled included PTPs with severe HA (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe HA), aged ≥12 years. In addition, subjects from Arm B (on-demand regimen) had to have at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrollment.

Previous treatment for HA (prophylaxis or on-demand regimen) was defined as any treatment with any recombinant and/or plasma-derived FVIII product or cryoprecipitate for at least 150 exposure days (EDs). Subjects with a history of a positive inhibitor test or with a positive inhibitor test result at screening were excluded.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study treatments included 50 IU/kg of IV BIVV001 as once-weekly prophylaxis or on-demand treatment. The product was administered as a lyophilized powder in a sterile vial that requires reconstitution with sterile water for injection (diluent).

6.1.5 Directions for Use

Prophylaxis was given once weekly. A single dose was given during a bleeding episode and additional and adjusted doses were given every two to three days if the bleeding episode did not improve. For minor bleeds, a decreased dose of 30 IU/kg could be given.

For perioperative use, a dose of 50 IU/kg was given.

6.1.6 Sites and Centers

The study was conducted worldwide in 19 countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Spain, South Korea, Taiwan, United Kingdom, and United States of America) at 51 active centers (defined as centers that screened at least one subject). Subjects were enrolled in 48 of the 51 active centers.

6.1.7 Surveillance/Monitoring

The trial was conducted in accordance with Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice. The 21 Code of Federal Regulations, parts 312, 50, and 56 were followed.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was ABR for patients receiving prophylaxis treatment.

As above, the key secondary endpoint included:

- Intrapatient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the ABR with historical prophylaxis for subjects in Arm A

Other secondary endpoints included:

- Intrapatient comparison of ABR during the once-weekly prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B

- ABR for all bleeding episodes
- Percentage of bleeding episodes treated with a single injection
- Joint bleeding rate
- Target joint resolution
- Hemostatic response for surgical procedures
- Occurrence of AEs, SAEs
- Development of Inhibitors, embolic and thrombotic events

Reviewer Comment: *Results related to treated and untreated bleeds are included in the label to demonstrate ABR of all bleeding events.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

The evaluation was based on the primary endpoint of ABR in adult and adolescent subjects receiving prophylaxis/on-demand treatment. The full analysis set (FAS) included subjects who received at least one dose of the study drug.
The primary analysis of the primary endpoint was the estimate of the mean ABR and one-sided 97.5% CI using a Negative-Binomial model for the weekly prophylaxis arm (Arm A) based on the FAS. If the upper limit of the CI is less than or equal to 6, the weekly prophylaxis treatment regimen will be considered to provide adequate bleeding control.

As noted in the statistical review memo:
The key secondary endpoint, the intra-subject comparison of ABR between ALTUVIIIO weekly prophylaxis and historical prophylaxis, were performed using a negative binomial regression model accounting for overdispersion with the dependent variable as "total bleeding episodes", covariate as "treatment regimen", repeated variable as "subject", and log time as an offset variable. The mean paired difference and 95% CI were estimated using the PPS (as primary analysis) and FAS (as supportive analysis).

6.1.10 Study Population and Disposition

In total, 170 subjects were screened for the study. Eleven subjects were not eligible per the screening criteria. A total of 159 subjects were enrolled: 133 in Arm A and 26 in Arm B. All subjects received at least one dose of BIVV001.

Of the 133 subjects in Arm A, 17 were enrolled in the sequential PK subgroup.

Thirteen subjects (12 in Arm A and 1 in Arm B) were included in the surgery subgroup.

Protocol deviations included administration of an expired drug product (n=9), concomitant medication use, and study conduct (missing study visits due to COVID pandemic). The deviations did not impact the overall conclusions of the study.

6.1.10.1 Populations Enrolled/Analyzed

This trial enrolled subjects with severe HA aged 12 to 72 years. There were 25 subjects between 12 and 17 years.

6.1.10.1.1 Demographics

The mean (SD) age of the subjects was 35.4 (15.1) years (range: 12 to 72 years); 25 (15.7%) subjects were between 12 and 17 years, 129 (81.1%) were between 18 and 64 years, and 5 (3.1%) were 65 years or older. Adolescents aged 12 to 17 years were all in Arm A. One female subject was enrolled; all the other subjects were male.

Reviewer Comment: *The female subject was enrolled in Arm A and was included in the efficacy evaluable population.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

At study entry, all subjects had a documented FVIII activity level below 1% or a documented genotype known to produce severe HA. All subjects had no history of a positive inhibitor (those with positive inhibitor test result at Screening were excluded). The majority of subjects (n=125 [78.6%]) had no family history of an FVIII inhibitor. The mean (SD) number of bleeding episodes reported during the 12 months prior to the study was 3.2 (5.4) in Arm A (prestudy on prophylaxis regimen) and 35.7 (22.2) in Arm B (prestudy with on-demand treatment).

At Baseline, of the 133 subjects in Arm A, 26 (19.5%) reported at least 1 target joint with a total of 80 reported target joints. Of the 26 subjects in Arm B, 23 subjects reported at least 1 target joint at Baseline.

6.1.10.1.3 Subject Disposition

A total of 149 subjects completed the study. Ten subjects prematurely discontinued treatment. The most frequently reported reasons for study discontinuation were the use of prohibited concomitant medication and consent withdrawn (3 [1.9%] subjects each). One subject in Arm A discontinued due to an adverse event (AE) of decreased CD4 lymphocytes. Reason for study discontinuation was death (pancreas cancer with multiple metastatic nodules in liver) for one subject in Arm B. Among the reasons for study discontinuation, “other” was reported in one subject and was related to the subject’s personal situation (subject moved abroad); protocol violation was reported in one subject and was related to the use of an FVIII product other than BIVV001 before the end of study.

6.1.11 Efficacy Analyses

The primary efficacy analysis was to evaluate the ABR for subjects receiving prophylaxis treatment in Arm A.

Reviewer Comment: *It was noted that since this product is given weekly, some subjects were not able to complete 50 EDs. Although this is acceptable given the extended half-life of BIVV001, the subject must have completed at least 6 months of treatment (26 weeks) to be included in the efficacy analysis. The efficacy analysis therefore focused on 128 subjects (efficacy evaluable set), and the package insert adequately notes the efficacy-evaluable population of 128 in Arm A.*

6.1.11.1 Analyses of Primary Endpoint(s)

Arm A

In the Full Analysis Set (FAS), a total of 86 bleeding episodes were treated with BIVV001 in 133 subjects. In both Arm A and Arm B, joints were the most common location for bleeds.

For the efficacy-evaluable population of Arm A (n=128), the mean ABR for all bleeds was 1.1 (95% CI 0.8, 1.5) and the median ABR (IQR) for all bleeds was 0 (0, 1.2). There were 71 subjects with 0 bleeds. The mean ABR for treated bleeds was 0.7 (95% CI 0.5, 1.0) and the median was 0 (0, 1.0).
The rates of spontaneous and traumatic bleeds were as follows:

a. The median for both was 0.
b. The mean annualized spontaneous bleeding rate (AsBR)(SD) was 0.29 (0.73) in Arm A.
c. The majority of subjects (81%) had no spontaneous bleeds.
d. The estimated mean annualized traumatic bleed rate (SD) was 0.36 (0.83) in Arm A.
e. There were 92 subjects with 0 joint bleeds.

Reviewer Comment: *As noted above, subjects with at least 26 weeks of exposure were included in the efficacy analysis, and therefore the efficacy analysis focused on the efficacy-evaluable population of Arm A (n=128).*

It is also important to note that information on both analyses (treated and all bleeds) are included in the label. The clinical reviewer believes that information on treated and nontreated bleeds is important to the prescribers. In addition, the reviewer recommends including the mean and median ABR to represent the observed effect. The upper bound of the 95% CI is lower than the pre-specified upper bound of six, which is favorable.

The pre-BIVV001 baseline FVIII prophylaxis was higher than compared to BIVV001. Of note, only 78 subjects were included in this analysis and only treated bleeding episodes were included. No additional details are provided on how compliant the study subjects were on previous FVIII therapy, but the baseline ABR rate is consistent with the other class of products.

Arm B

- For the 26 subjects in Arm B, ABR with BIVV001 prophylaxis was compared with on-demand treatment. The median ABR during the on-demand period was 21.13 compared with 0 for the prophylaxis period.
- In Arm B, the estimated mean AsBR decreased after subjects switched to prophylaxis treatment (0.44 [95% CI: 0.16, 1.20]) as compared with on-demand treatment (15.83 [95% CI: 12.27, 20.43]).
- With on-demand treatment, most subjects (80.8%) had an AsBR greater than 5 and 7 (26.9%) subjects had an AsBR greater than 20; after switching to prophylaxis treatment, most subjects (84.6%) had no spontaneous bleeds, and no subjects had an AsBR greater than 5.

Reviewer Comment: *All subjects in Arm B had at least 26 weeks (6 months) of treatment with the study product. As expected, subjects treated on demand with this product continued to have increased ABRs as compared with prophylaxis. There was not a reduction in ABR using this product on demand, which validates the benefit of routine prophylaxis for reduction of bleeding events in patients with hemophilia A.*

Perioperative Use

Subjects who underwent major surgery were included in the surgery subgroup analysis. A total of 14 major surgeries were performed in 13 subjects in both treatment arms; however, only 12 surgeries were assessed. All were in Arm A except one subject. One subject underwent 2 major surgeries.

Reviewer Comment: *Two surgeries occurred after the last BIVV001 dose and were not included in the assessments of major surgeries. Therefore, only 12 major surgeries were assessed in the adult/adolescent study. An additional major surgery in the pediatric surgery was assessed to include 13 major surgeries.*

For the 12 major surgeries assessed, all 12 had an assessment of excellent by the Investigator/Surgeon. Eleven surgeries required a single preoperative injection of BIVV001 to maintain hemostasis. For one surgery, no preoperative dose was given. The mean (SD) number of BIVV001 injections was 1.0 (0.0) during major surgery (Days -1 to 0), 1.1 (0.4) immediately following surgery (Days 1 to 3), 2.4 (0.7) for Days 4 to 14 following surgery, and 3.8 (1.5) for the first 14 days following the surgery, including the loading dose.

The mean (SD) estimated blood loss was 143 ml (189) during major surgery for the six subjects whose information was reported. Postoperatively, this information was reported for nine subjects. Six subjects had no postoperative blood loss and three had blood loss of 90-400 ml. No subject required transfusion during the surgical period.

Reviewer Comment: *The surgeon's assessment was made during the intraoperative period and early during the postoperative time period. The subjects had appropriate blood loss for various major surgeries (400 ml of blood loss in hip replacement surgery). Most subjects resumed routine prophylaxis on Days 4 to 7 postoperatively. The clinical reviewer agrees with these assessments as postoperatively on Days 1 to 3 there was minimal use of BIVV001. On Days 4 to 14, the use increased as subjects required another dose postoperatively and then transitioned back to their routine prophylaxis regimen. For one surgery, there was no preoperative dose given.*

In the ongoing extension study, there is a separate cohort to assess perioperative management. This study was not evaluated for initial licensure of this product as the study is ongoing and the complete data have not been submitted. An additional eight surgeries have been evaluated and appear to have similar outcomes based on a limited review.

6.1.11.2 Analyses of Secondary Endpoints

Intra-subject historical controls were used in this study. The baseline ABRs of subjects prior to BIVV001 administration were used for comparison to post treatment with BIVV001 and was a key secondary endpoint. For this key secondary endpoint, non-inferiority of the intra-subject comparison of ABR between BIVV001 weekly prophylaxis

and historical prophylaxis, was demonstrated (estimated mean difference in ABR of -2.30 (95% CI, -3.49, -1.11).

For the subjects who had prophylaxis history prior to initiation of BIVV001 and were in the efficacy evaluable set (n=78), these subjects had a median ABR of 1.07 (0, 3.7) compared with the improved ABR rate with administration of BIVV001. The pre-BIVV001 administration baseline FVIII prophylaxis Mean ABR (95% CI) (n=78) was 2.99 (2, 4.4) compared to a Mean ABR of 0.69 (0.43; 1.12) following administration of BIVV001.

In Arm A, 102 subjects (with evaluable FVIII levels) maintained activity above 5% and 86 (84%) maintained FVIII activity levels above 10% for 7 days after dosing. Maintenance of FVIII levels above 15% were observed in 42 (41%) subjects.

Overall, there were 375 injections to treat 362 bleeds. All but one bleeding episode were controlled with fewer than two injections of BIVV001; 97% were controlled with one injection. No bleeding episodes required more than three injections. Of these injections, 334 were evaluated for response, with the majority rated as producing an excellent or good response (n=317; 84.5%).

Reviewer Comment: *One subject required three injections for a traumatic bleeding episode over four days and was given approximately 50 IU/kg at onset, approximately 30 IU/kg two days later, and subsequently 50 IU/Kg two days later with resolution. The subject took a dose four days later for an unknown bleed. He had third bleed a week later and a subsequent fourth bleed four days later and received BIVV001 with resolution.*

Overall, the vast majority of bleeding events were controlled with one dose of BIVV001. The clinical reviewer agrees with the assessment above regarding the adequacy of hemostasis.

The results for annualized joint bleeding rate (AJBR) were consistent with the results for ABR. In Arm A, 37 subjects had a total of 61 treated joint bleeds and 96 subjects had no joint bleeds during the study. There were 14 subjects who had at least 12 months of continuous exposure to BIVV0001 with 45 target joints and all resolving after 1 year of exposure.

In Arm B, the mean AJBR was higher with on-demand compared with prophylaxis treatment, 17.48 and 0.62, respectively.

6.1.11.3 Subpopulation Analyses

A subpopulation analysis was conducted on the mean treated ABR on the FAS. The treatment effects were consistent across subgroups based on age categories, baseline bleeding phenotype, number of target joints at screening or dosing and dosing interval compliance and were consistent with the primary endpoints.

6.1.11.4 Dropouts and/or Discontinuations

There were 10 subjects who prematurely discontinued. The most frequently reported reasons for study discontinuation were the use of prohibited concomitant medication and consent withdrawn (3 [1.9%] subjects each). One subject in Arm A discontinued due to an AE of CD4 lymphocytes decreased (see Section 5.2.2.3). Reason for study

discontinuation was death (pancreas cancer with multiple metastatic nodules in liver) for one subject in Arm B (see Section 5.2.2.1). Among the reasons for study discontinuation, “other” was reported in one subject and was related to the subject’s personal situation (subject moved abroad); protocol violation was reported in one subject and was related to the use of an FVIII product other than BIVV001 before the end of study

6.1.11.5 Exploratory and Post Hoc Analyses

In Arm A, the mean (SD) Hemophilia Joint Health Score (HJHS) total score at baseline in subjects on a stable prestudy prophylaxis treatment was 18.1 (18.4). The estimated mean change in HJHS total score from baseline to Week 52 indicated improvement in functional measure of joint health.

Quality-of-life data were collected in adult subjects aged ≥17 years via the Haem-A-QoL questionnaire and in adolescent subjects aged 12 to 16 years via the Haemophilia-Specific Quality of Life Questionnaire, or Haemo-QoL. These demonstrated an improvement in physical health.

PROMIS data were collected in all subjects for pain intensity and separately in subjects ≥18 years and in those <18 years for pain interference and physical health and demonstrated an improvement in pain.

These measurements were evaluated by the Center for Drug Evaluation and Research (CDER) patient-reported outcome (PRO) team. The PRO-based secondary efficacy endpoint results (Haem-A-QoL physical health [PH] and PROMIS Pain Intensity 3a Item 1 [Worst Pain]) from Study EFC16293 were challenging to interpret (b) (4)

1. The open-label nature of the XTEND-1 study (Study EFC16293) design may have led to biased responses for the PRO measures (i.e., patients’ knowledge of treatment assignment is likely to influence how they report information on the PRO) and, subsequently, to biased estimates of treatment effect.
2. Exit interviews used to support clinically meaningful within-patient changes for the PRO-based secondary efficacy endpoints were optional (i.e., convenience sample) and the sample selection may have led to biased responses.
3. Quantitative anchor-based analyses and results from the exit interviews suggested that “no change” as measured by the PRO instruments may also be considered important and meaningful to patients; this patient perspective is inconsistent with the Applicant’s proposed labeling language in which an observed improvement is conveyed for physical function as measured by the Haem-A-QoL PH subscale and for worst pain as measured by the PROMIS Pain Intensity 3a (Worst Pain) item.
4. Lack of sensitivity due to a floor effect (i.e., patients do not have sufficient symptom/functional impairment) was observed on the Haem-A-QoL PH subscale and PROMIS Pain Intensity 3a (Worst Pain) item scores for Arm A at baseline, and a small magnitude of change in the PRO secondary endpoint scores at Week 52.
5. The range of clinically meaningful within-patient change thresholds was derived, in part, by distribution-based methods. Distribution-based approaches are inappropriate as a primary method for the evaluation of clinically meaningful within-patient change as they do not account for the patient voice and/or perspective.

Reviewer Comment: *These PRO data assessed by the CDER COA review team show that the data are challenging to interpret given identified limitations in the context of a single-arm study. Although the data may appear promising, there is uncertainty in the results as they may be biased.* (b) (4)

6.1.12 Safety Analyses

6.1.12.1 Methods

All evaluations of safety were based on the FAS (n=159).

6.1.12.2 Overview of Adverse Events

In total, there were 394 AEs experienced by 123 subjects. In the surgery subgroup, three AEs were reported in one subject. One subject experienced an AE leading to death and two subjects experienced AEs leading to treatment discontinuation. The subjects who discontinued treatment included one with a serious adverse event (SAE) of decrease in CD4 lymphocytes that was assessed as related. One subject had an SAE of a fracture that was assessed as not related.

Reviewer Comment: *It is unlikely that BIVV001 caused either of these SAEs that led to discontinuation. The clinical reviewer assessment is that these are not related to the product.*

The most commonly reported (>10% of subjects overall) treatment-emergent adverse events were headache, arthralgia, and back pain. The following are the most commonly reported TEAEs in the following system organ classes:

- Musculoskeletal and connective tissue disorders (n=56 [35.2%]); the most common was arthralgia (16.4%).
- Nervous system disorders (n=43 [27.0%]); the most common was headache (20.1%).

The following were reported with AEs less than 10%.

- Musculoskeletal and connective tissue disorders (n=56 [35.2%]) including back pain, arthropathy, and pain.
- Nervous system disorders (n=43 [27.0%]) including dizziness.
- Injury, poisoning, and procedural complications (n=30 [18.9%]) including fall, contusion, join injury and limb injury.
- Infections and infestations (n=34 [21.4%]) including nasopharyngitis, and upper respiratory tract infection.
- General disorders and administration site conditions (n=20 [12.6%]) including fatigue, influenza like illness, and vaccination site pain.
- Gastrointestinal disorders (n=22 [13.8%]) including toothache, and gastroesophageal reflux disease, and abdominal pain.
- Investigations (n=18 [11.3%]) including factor VIII level increase, bilirubin increase, GGT increase and SARS-COV-2 positive.

Reviewer Comment: *The AEs reported in the surgery subjects included infusion site rash, tooth fracture, and synovial disorder. All were reported as mild and not related to BIVV001. The clinical reviewer agrees with this assessment.*

6.1.12.3 Deaths

There was one death that occurred for a subject with a history of hepatitis C virus and who died of metastatic pancreatic carcinoma. This event was assessed as not related to the study product, and this reviewer agrees with this assessment.

6.1.12.4 Nonfatal Serious Adverse Events

Of the 159 subjects, 15 subjects had 18 SAEs (16 in Arm A, 2 in Arm B). These included neoplasms, nervous system disorders, cardiac disorders, musculoskeletal events, lab abnormalities, and fracture.

Reviewer Comment: *All SAEs reported were mild to moderate in severity and this reviewer agrees that they were not related to the product. For the lab abnormalities, one included a CD4 lymphocyte decrease in a subject with HIV. BIVV001 was discontinued. The fracture also resulted in discontinuation of use and another FVIII product was used.*

6.1.12.5 Adverse Events of Special Interest

Inhibitor development to FVIII was defined as a neutralizing antibody value ≥0.6 BU/mL confirmed by a second test result of ≥0.6 BU/mL from a separate sample, drawn two to four weeks following the date when the original sample was drawn. Both tests had to be performed by the central laboratory using the (b) (4) Bethesda assay.

There were no reports of inhibitor development to FVIII during the study.

There were 14 subjects who tested positive for antidrug antibodies (ADAs) at one or more timepoints (9 in arm A; 5 in Arm B).

- Three participants had ADAs directed against the FVIII moiety of BIVV001.
- Two participants showed ADAs against the human Fc moiety of BIVV001.
- Two participants tested positive for anti-XTEN antibodies.
- One participant had ADAs directed against the D´D3 moiety of BIVV001.
- Eight participants tested negative for ADAs against all the moieties of BIVV001 (FVIII, huFc, XTEN, D´D3) at all ADA positive timepoints.

Reviewer Comment: *As these subjects were previously treated, it is reassuring that there was no inhibitor development to this naïve product.*

For those subjects with positive ADAs, only four had cases that were considered treatment induced and 10 were positive prior to BIVV001 dosing without titer increase throughout the study.

Of the three subjects with ADAs against FVIII, the FVIII activity was not lower and were negative for inhibitors. Although these findings did not produce any change in FVIII and ultimately on the clinical endpoint of ABR, it is important to note that these events do occur. This will be included in the label.

There were no reports of Grade 3 or greater allergic reactions or anaphylaxis with BIVV001 administration. There were six events of hypersensitivity in four subjects, including four events of skin rash and contact dermatitis at infusion site, a wrist rash, and upper lip angioedema. None were assessed by the investigator and applicant as related and all resolved.

Reviewer Comment: *One skin rash occurred after needle removal, one was with another drug administered; no further details of the contact dermatitis at injection site were provided but the case was mild and resolved. The wrist rash was mild and resolved. The upper lip angioedema was moderate in severity but was not temporally related to administration of the study drug. The clinical reviewer can't definitively conclude that these are not related to the injection procedure. These events were mild and transient and do not raise safety concerns. Case report reviews and reviews of narratives for subjects with hypersensitivity reaction did not identify any subjects who experienced an anaphylactic reaction.*

There were no reports of embolic and thrombotic events during the study. However, in the 120-day safety update report, there were three subjects who had thrombotic events. One subject had a deep vein thrombosis after a femur fracture and post orthopedic immobilization, one subject had a right-hand hemangioma and thrombosis, and the third has a cerebral infarct. All subjects had other risk factors for these events, but the study drug likely increased the risk for thrombosis to develop.

Reviewer Comment: *All three subjects with thrombotic events had other risk factors including immobilization post-surgery, vascular malformation, and atrial fibrillation. Although these risks are present, the addition of this product may have compounded the risk for significant events. Therefore, Section 6 of the label will be updated with inclusion of these events.*

6.1.12.6 Clinical Test Results

There were no clinically meaningful lab trends in any of the laboratory parameters to include hematology and chemistry panel testing. There were no clinically meaningful lab trends for von Willebrand ristocetin cofactor or VWF antigen.

6.1.12.7 Dropouts and/or Discontinuations

One subject with HIV had a decrease in CD4 lymphocytes that resulted in discontinuation of BIVV001. The decreased CD4 is attributed to the underlying HIV and not deemed related to BIVV001

6.1.13 Study Summary and Conclusions

Prophylactic infusion with BIVV001 was effective for prevention of bleeds at weekly dosing intervals as compared with on-demand treatment.

Most bleeds were treated with 1 infusion and hemostasis was judged to be excellent or good. The study drug provided 'excellent' hemostatic control during 12 major surgeries in adults and adolescents with severe HA. The blood loss was within expected ranges.

No subject developed inhibitory antibodies to FVIII during the study. No unexpected AEs occurred, and the most commonly reported AEs were headache, arthralgia, and back pain, and were mild and transient. Three events of thrombosis occurred, but these risks are expected and will be discussed in the label. Overall, BIVV001 exhibited a favorable safety and tolerability profile.

6.2 Trial #2

Study EFC16295: This is an ongoing Phase 3 open-label, multicenter study of the safety, efficacy, and PK of IV BIVV001 in previously treated pediatric patients <12 years with severe HA

6.2.1 Objectives (Primary, Secondary, etc)

Primary: To evaluate safety in previously treated pediatric subjects

Key secondary objectives include efficacy evaluation of BIVV001 as a prophylaxis treatment and in the treatment of bleeding episodes, consumption, the effect of join health outcomes, perioperative management, and quality of life outcomes.

6.2.2 Design Overview

Subjects were in two age cohorts (<6 years and 6 to <12 years) and received BIVV001 for approximately 52 weeks to reach 50 EDs. PK evaluation was performed on a subset of subjects.

Reviewer Comment: *At the time of data cutoff (January 2022), the study was ongoing. These interim analysis data were the basis of the review for the pediatric indication as agreed upon at the pre-BLA meeting. Please refer to the Clinical Pharmacology memorandum for complete details of the PK in pediatrics.*

6.2.3 Population

Th study population included PTPs <12 years with severe HA (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe HA). Subjects with a history of a positive inhibitor test or with a positive inhibitor result at screening were excluded.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study is comprised of two age cohorts (<6 years and 6 to <12 years), and subjects received IV BIVV001 at a dose of 50 IU/kg once weekly for 52 weeks.

6.2.5 Directions for Use

Prophylaxis treatment with 50 IU/kg was given once weekly. During a bleeding episode, a single dose was administered with additional and adjusted doses given every two to three days if the bleeding episode did not improve. For minor bleeds, a decreased dose of 30 IU/kg could be given.

For perioperative use, a dose of 50 IU/kg was given.

Reviewer Comment: *Please refer to the Clinical Pharmacology review for further details on pediatric dosing and clearance. Although higher clearance was noted in the pediatric population, dosing was not adjusted as the clinical endpoint of ABR remained adequate.*

6.2.6 Sites and Centers

The study is being conducted worldwide in 15 countries/regions (United States of America, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain,

Sweden, Switzerland, United Kingdom, Turkey, Australia, and Taiwan) at 38 active centers (defined as centers that screened at least one subject).

6.2.7 Surveillance/Monitoring

The trial was conducted in accordance with Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice. The 21 Code of Federal Regulations, parts 312, 50, and 56 were followed.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint is the occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the (b) (4) Bethesda assay). Inhibitor development was defined as an inhibitor result of ≥0.6 BU/mL that is confirmed by a second test result from a separate sample, drawn two to four weeks following the date when the original sample was drawn.

An interim analysis of key safety, PK, and selected efficacy endpoints was performed at the time of the completion of the pivotal Phase 3 study in adults and adolescents (Study EFC16293). The efficacy endpoint of ABR was analyzed using the FAS including subjects with an efficacy period of at least 26 weeks.

6.2.9 Statistical Considerations and Statistical Analysis Plan

The efficacy endpoint of ABR was analyzed using the FAS, including subjects with an efficacy period of at least 26 weeks. The mean and 95% CI of ABR was estimated using a negative-binomial model. The model included the number of treated bleeding episodes during the efficacy period.

Reviewer Comment: *Although treated bleeds are informative, all bleeds (treated and untreated) give a comprehensive ABR of a subject and were analyzed as the primary endpoint by this reviewer and will be included in the label.*

6.2.10 Study Population and Disposition

The FAS is comprised of all subjects who received at least one dose of BIVV001. The per protocol set are all subjects evaluated for the efficacy endpoint.

6.2.10.1 Populations Enrolled/Analyzed

A total of 73 subjects were screened for the study. At the data cut-off date, a total of 67 subjects were enrolled in the single arm of this open-label study and received at least one dose of BIVV001, including 31 in the <6 years cohort and 36 in the 6 to <12 years cohort.

The safety analysis set, and FAS were composed of 67 (100.0%) subjects who received at least 1 injection of BIVV001. The FAS included 63 (94.0.%) subjects who received at least 2 prophylactic injections, of whom 27 were in the <6 years cohort and 36 in the 6 to <12 years cohort.

A total of 32 subjects from the 2 age cohorts were enrolled in the PK subgroup and were evaluable, including 14 in the <6 years cohort and 18 in the 6 to <12 years cohort.

6.2.10.1.1 Demographics

The mean (SD) age of subjects was 6.24 (2.93) years. In the <6 years cohort, the mean (SD) age was 3.72 (1.27) years (range: 1.4 to 5.0 years); in the 6 to <12 years cohort, the mean (SD) was 8.42 (2.08) years (range: 6.0 to 11.0 years). The majority of subjects were not Hispanic, or Latino (92.5%) and the majority were White (75%).

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The mean (SD) age at the start of first prophylactic treatment was 1.0 (1.1) years (range: 0 to 5 years). The mean (SD) number of bleeding episodes reported in the 12 months prior to the study was 2.3 (4.4) across the overall study population. Nineteen (30.6%) subjects reported no bleeds during the past 12 months. No target joints were reported at baseline in 65 (97.0%) subjects.

All subjects, except one, were on prophylactic treatment.

In the 12 months prior to the study, the mean (SD) total number of bleeding episodes on a prophylactic regimen was 2.3 (4.4) across the overall study population. The majority of subjects experienced 5 or fewer bleeding episodes (n=39 [62.9%]) or no bleeding episode (n=19 [30.6%]).

6.2.10.1.3 Subject Disposition

At the data cut-off date, none of the subjects had completed the study, and 66 subjects' participation in the study was ongoing, and 1 subject withdrew from the study.

One subject had one major surgery and four subjects had four minor surgeries.

Overall, the mean (SD) total exposure to BIVV001 was 19.3 (14.9) EDs: 16.3 (15.1) EDs in the <6 years cohort, and 22.0 (14.5) EDs in the 6 to <12 years cohort.

Twenty-three (34.3%) out of 67 study subjects achieved at least 25 EDs: 11 (35.5%) subjects in the <6 years cohort and 12 (33.3%) in the 6 to <12 years cohort.

Reviewer Comment: *For the primary endpoint of safety, and in particular inhibitor development, naïve subjects will develop an inhibitor within the first 10 to 15 EDs. This patient population is composed of PTPs who are naïve to this product. Therefore, it is reassuring that the majority of the overall population studied crossed this threshold of exposure.*

6.2.11 Efficacy Analyses

There were 63 subjects in the efficacy evaluable period who received BIVV001 weekly who were compliant to the dosing and the dosing interval.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was ABR for treated bleeds and all bleeding episodes. The efficacy analysis was a secondary objective.

For the interim analysis of efficacy, secondary endpoints were evaluated for routine prophylaxis and for the treatment of bleeding episodes in children <12 years.

The interim analysis of the efficacy endpoint of ABR was performed on subjects with an efficacy period of at least 26 weeks, which included 23 subjects. There were 11 subjects <6 years and 12 subjects 6 to <12 years.

Treated Bleeds: The overall mean estimated ABR in 23 subjects with an efficacy period at least 26 weeks was 0.54 (95% CI: 0.23, 1.26) with a median ABR of 0.00 (IQR: 0.00,1.27).

Intra-subject historical control data (one year prior to BIVV001 administration) were used to assess and compare baseline ABR pre- BIVV001 and after BIVV001 administration. The baseline mean (SD) treated ABR was 1.7 (2.1) and median (IQR) of 1.0 (0; 8).

Treated and Untreated Bleeds: The overall mean estimated ABR in 23 subjects with an efficacy period at least 26 weeks was 3.6 (95% CI: 1.6, 8.4) with a median ABR of 0 (IQR: 0, 4.5).

Evaluating all subjects with an efficacy evaluable period revealed that no bleeding episodes were reported by most (17 of 23 subjects with at least a 26-week efficacy period and 52 of 63 subjects overall).

A total of 9 treated bleeding episodes were reported in 6 of the 23 subjects. Overall, a total of 19 bleeding episodes were treated with BIVV001. There were 13 traumatic bleeds, 3 spontaneous bleeds, and 3 with status unknown. Overall, 100% of bleeding episodes were controlled with one or two injections. Sixteen (84.2%) bleeding episodes resolved with a single dose of BIVV001. The hemostatic response was rated as excellent for 12 of the 13 evaluable episodes. Of the 38 subjects with FVIII activity assessments, all maintained levels above 3%. Eleven subjects maintained FVIII levels above 10% per week post dose.

Reviewer Comment: *The low ABR for treated bleeds in the pediatric population demonstrates the efficacy of this product with sustained FVIII levels. Although the PK parameters show a higher clearance in the pediatric population, sustained FVIII levels have decreased bleeding events.*

In the efficacy-evaluable population, there were six subjects with bleeding episodes, one of whom had an ABR of 4.9. This subject had three traumatic bleeds and a skin/mucosal bleed and was given one dose of BIVV001 for these four bleeds. All the bleeding events occurred five to seven days after the previous prophylactic injection of BIVV001 and responses were excellent. It is reassuring that these were not spontaneous bleeding events.

At this time for the interim analysis, the ABR rate is observed to be reduced compared to the baseline bleeding rate in the efficacy evaluable population. The final data for all subjects at the completion of the study will provide robust data.

Based on all bleeding event ABR data, it appears there were more untreated bleeding events. There were eight subjects with a higher all bleed ABR than ABR for treated bleeds. There were seven subjects with an all bleeds ABR over 2. A total of 47 untreated bleeds were reported by the caregivers. There were 28 bleeds that were reported in one subject. This subject did not have any treated bleeds. Most of these untreated bleeds included epistaxis and mucocutaneous bleeds. It is unclear why these bleeding events

were not treated especially after multiple events, but reported as mild and self-resolving in this 5 year old subject. Although the increased mean ABR (3.6) is noted, a sensitivity analysis excluding this one subject results in a mean ABR of 2.6, which is comparable to other products. Completion of this study will provide additional details on the ABR for all bleeds.

6.2.11.2 Analyses of Secondary Endpoints

Perioperative Management

One subject in the <6 years cohort underwent a major surgery of molar extraction. The subject received a preoperative dose of BIVV001 at 61.9 IU/kg. Postoperative Day 3, another lower dose of BIVV001 at 31.7 IU/kg was given and then resumed once weekly as prophylaxis. The investigator assessment was rated as excellent. No transfusions were given. Four minor surgeries were performed in the pediatric population.

6.2.11.3 Subpopulation Analyses

PK was evaluated by both chromogenic and one-stage assay for age groups <6 years (n=14) and 6 to <12 years (n=18).

Greater BIVV001 clearance was associated with lower subject age. With weekly dosing of BIVV001, pediatric subjects <6 years had a lower trough level, area under the concentration-time curve, and days with FVIII activity >40 IU/dL compared with subjects in other age groups.

Reviewer Comment: *Although clearance was greater with lower age, BIVV001 maintained FVIII activity above 40 IU/dL for up to 3 days. These levels translated to reduced treated bleeds. The effect of age on bleeding risk is not well described as bleeding risk is influenced by several factors.*

6.2.11.4 Dropouts and/or Discontinuations

One subject discontinued due to a positive inhibitor titer at the baseline visit. It was determined that he no longer meet eligibility criteria and was withdrawn from study. He had received three doses of BIVV001. The positive titer returned to being negative. No other subject discontinued.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety was evaluated in all subjects who received at least one dose of BIVV001. The primary endpoint of this study was the occurrence of inhibitor development to FVIII.

6.2.12.2 Overview of Adverse Events

There were 75 AEs in 36 subjects. There were 40 AEs in 20 subjects <6 years and 34 AEs in 16 subjects 6 to <12 years. In the surgery subgroup, one AE was reported for the

only patient who underwent major surgery. The most commonly reported AEs (>5%) were upper respiratory tract infections, nasopharyngitis, pyrexia, and cough. There were no major differences in AEs reported between the two age groups. All AEs were either mild or moderate in severity. There were no AEs classified as severe.

Reviewer Comment: *All AEs were assessed as not related to BIVV001. The clinical reviewer agrees with this assessment. The classification of the AEs appears appropriate. One AE of cheilitis was reported during surgery and was not related to BIVV001.*

6.2.12.3 Deaths

There were no deaths in the pediatric subjects.

6.2.12.4 Nonfatal Serious Adverse Events

There were no SAEs.

6.2.12.5 Adverse Events of Special Interest

Inhibitor development was not detected. There were no reports of Grade 3 or higher serious allergic reaction or anaphylaxis. There were no vascular thrombotic events. There were no reports of overdose.

There were 23 subjects who were evaluated for ADAs. A total of three subjects had positive ADA at screening before receiving BIVV001. These ADAs were positive against different moieties in the product and were transient. There was no clinical manifestation of these ADAs.

Reviewer Comment: *There were no reports of inhibitors in this PTP population as most have crossed the threshold of 10 to 15 EDs with BIVV001.*

There were reports of minor allergic reactions and all were assessed by the clinical reviewer as unrelated to the product. One subject had a severe allergic reaction after data cut off which included hives after eating chocolate and was treated with epinephrine. This occurred 3 days after the last dose of BIVV001. This is likely not related to the product.

It is unclear why there is a presence of ADAs prior to treatment. It is reassuring that these antibodies are transient and have no clinical effect.

6.2.12.6 Clinical Test Results

There were no clinically meaningful patterns or trends observed in hematologic parameter changes over time in either age cohort. There were no clinically meaningful patterns or trends observed in chemistry parameter changes over time in either age cohort. There were no clinically meaningful patterns or trends observed in von Willebrand panel changes over time in either age cohort.

6.2.12.7 Dropouts and/or Discontinuations

There were no SAEs and no AEs that resulted in death or led to treatment discontinuation.

6.2.13 Study Summary and Conclusions

The interim results from this study show that once-weekly IV BIVV001 at 50 IU/kg was well tolerated and effective as routine prophylaxis to protect against bleeding episodes in PTPs <12 years with severe HA. In addition, BIVV001 was effective for the control of bleeding episodes and provided hemostatic efficacy during a surgical procedure. The most commonly reported AEs were upper respiratory tract infections, nasopharyngitis, pyrexia, and cough and were mild and transient. There were no inhibitors detected thus far and no new safety signals in the pediatric population. Overall, available data support the use of BIVV001 in pediatric patients with HA.

Reviewer Comment: Of note, the statistical reviewer is unable to support the conclusion of safety with respect to inhibitor development in this population given that none of the subjects reached at least 50 EDs, which was the pre-defined primary analysis population for the primary analysis of inhibitor incidence and deferred the decision to the clinical reviewer on the acceptance of the interim data supporting the pediatric indication.

Inhibitor development for a PTP population is rare. As stated above, although these subjects are naïve to this product, they have crossed the initial inhibitor development threshold of 10-15 EDs. At the completion of the study, any inhibitor development will be addressed in the label. Further pharmacovigilance surveillance will be done post approval for development of inhibitors which will also be updated in the label. The adult and adolescent data also support that this PTP population has not reported inhibitor development. This clinical reviewer does not agree that this lack of information should preclude approval for this product for the pediatric indication.

7. Integrated Overview of Efficacy

7.1 Indication #1

7.1.1 Methods of Integration

Integration of the pediatric study with the adult and adolescent data was not done because of the differences in study designs. Integration is challenging, and therefore, the data for each study are summarized and presented separately.

7.1.2 Demographics and Baseline Characteristics

Refer to Section 1.1 for Demographics of all subjects treated with BIVV001.

7.1.3 Subject Disposition

All subjects had severe HA and were PTPs.

7.1.4 Analysis of Primary Endpoint(s)

Efficacy was based on ABR. The mean ABR for all bleeds was 1.11 (95% CI: 0.83, 1.48) and median (Q1, Q3) ABR for all bleeds was 0 (0, 1.2) in the adult/adolescent study. In the pediatric study, for all bleeds, the mean ABR was 3.6 (95% CI: 1.6, 8.4) and the median (Q1, Q3) ABR was 0 (0, 4.5).

7.1.5 Analysis of Secondary Endpoint(s)

N/A

7.1.6 Other Endpoints

N/A

7.1.7 Subpopulations

N/A

7.1.8 Persistence of Efficacy

N/A

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

The basis of FDA's conclusion of substantial evidence of effectiveness comes from two adequate and well-controlled trials utilizing intra-patient historical control data in adult and pediatric subjects with clinically meaningful benefit in ABR during the efficacy-evaluable period.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety of BIVV001 was evaluated in a total of 126 PTPs with severe HA (159 adult and adolescent subjects [12-17 years] and 67 pediatric subjects [<12 years of age]).

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety dataset included all subjects who received at least one dose of BIVV001, which included subjects from the adult and adolescent study and the pediatric study.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In the adult/adolescent and pediatric study, 177 completed at least 26 weeks of exposure. In the adult and adolescent study, 115 subjects received at least a total number of 50 EDs in Arm A and 17 subjects completed at least 25 EDs of routine prophylaxis in Arm B.

8.2.3 Categorization of Adverse Events

N/A

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Although the results across all studies were pooled, the study designs were different.

8.4 Safety Results

8.4.1 Deaths

One adult subject died of pancreatic carcinoma that was unlikely related to BIVV001. There were no deaths in the pediatric study.

8.4.2 Nonfatal Serious Adverse Events

There were no SAEs reported in the pediatric study. The SAEs reported in the adult adolescent study are described in Section 6.1.12.4.

8.4.3 Study Dropouts/Discontinuations

As above.

8.4.4 Common Adverse Events

The most common adverse events were headache, arthralgia, and back pain.

8.4.5 Clinical Test Results

Overall, no clinically relevant changes associated with exposure to BIVV001 have been observed for laboratory parameters.

8.4.6 Systemic Adverse Events

See individual study sections.

8.4.7 Local Reactogenicity

N/A

8.4.8 Adverse Events of Special Interest

No subjects were reported to have developed FVIII inhibitors. There were three subjects, with pre-existing risk factors, who developed thrombosis during the extension study. There were no Grade 3 hypersensitivity reactions. See Section 6 for details.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

N/A

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

N/A

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.5.8 Immunogenicity (Safety)

No subject developed neutralizing antibodies to FVIII. Seventeen subjects developed transient anti-drug antibodies to different moieties of the product with no clinical consequence. Only four subjects had ADAs after receiving BIVV001.

8.5.9 Person-to-Person Transmission, Shedding

N/A

8.6 Safety Conclusions

The most commonly reported AEs were mild and transient. No FVIII inhibitor development was observed in the safety-evaluable population. No deaths related to BIVV001 occurred. One adult subject died of pancreatic cancer which is considered by the reviewer as unlikely related to BIVV001. No anaphylactic allergic reactions related to BIVV001were observed and no clinical consequence of ADAs were noted. Three thrombotic events were reported in subjects with pre-existing risk factors. The safety profile of BIVV001 for the proposed indications is favorable.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Based on the rare occurrence of HA in women, experience regarding the use of FVIII during pregnancy and breastfeeding is not available.

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

This application is exempt from PREA because it is intended for a biologic product for which orphan designation has been granted. The results of the interim analysis from Study EFC16295 provide persuasive evidence of clinical benefit in the pediatric population (see Section 6.2 above).

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use

N/A

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

Overall, BIVV001 demonstrated efficacy in adults and children for on-demand treatment to control bleeding episodes, perioperative management of bleeding, and routine prophylaxis. No treatment-related deaths were observed. No new safety signals were observed in the safety-evaluable pediatric, adolescent, and adult subjects.

FVIII inhibitors and allergic reactions will be communicated in the Warnings and Precautions sections of the label as potential risks.

The safety and efficacy of BIVV001 has been demonstrated for the following indications in adults and children:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See Table 5.

Table 5. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a rare hereditary bleeding disorder characterized by recurrent bleeding which, if untreated, leads to synovitis, chronic arthropathy, muscular atrophy, and deformities. • Treatment of bleeds may delay these complications but does not prevent them. • Primary prophylaxis with regular FVIII injections initiated at an early age is now the standard of care for patients with severe hemophilia A. • The frequency of bleeding in hemophilia A is generally inversely correlated with the FVIII activity level.	• Hemophilia A is a hereditary, serious, and life-threatening disease. • Hemophilia A can have a debilitating impact on physical and psychosocial well-being.
Unmet Medical Need	• There are several FVIII products licensed by FDA, both recombinant and plasma derived. • Plasma-derived products carry a potential risk of transmission of infection; all products carry the risks of inhibitor formation leading to ineffective therapy and hypersensitivity.	• Development of products with greater incremental recovery, good hemostatic coverage, and extended half-life is desirable. • Less frequent injections may reduce the burden of treatment.
Clinical Benefit	• BIVV001 has demonstrated an extended half-life. • Two trials to evaluate the efficacy of BIVV001 in adults/adolescents and children were provided. The efficacy was demonstrated for treatment of and prevention of bleeding events in patients with hemophilia A. • BIVV001 was effective in the perioperative setting for reduction of bleeding during surgery.	• The evidence for clinical benefit is shown in reduction of bleeds.
Risk	• The identified risks of FVIII replacement therapy are the development of FVIII inhibitors, thrombosis, and allergic reactions. • In the clinical trials, no previously treated patient developed FVIII inhibitors. • No Grade3 or higher hypersensitivity reactions were reported. • Thrombotic events were reported in 3 subjects with pre-existing risk factors.	• The risk of inhibitor development and allergic reactions is comparable to other FVIII products. • BIVV001 was well tolerated with no unexpected safety issues.
Risk Management	• The most substantial risks of treatment with BIVV001 are the development of FVIII inhibitors and hypersensitivity. • The pediatric study is ongoing.	• The package insert and routine pharmacovigilance activities are adequate to manage risk. • The final pediatric data will be reviewed with updates to the label.

Abbreviations: FDA, Food and Drug Administration; FVIII, coagulation factor VIII; PUP, previously untreated patients.

11.2 Risk-Benefit Summary and Assessment

The benefits of BIVV001 include:

- On-demand BIVV001 is effective for treatment of and prevention of spontaneous or traumatic bleeding in patients with HA
- BIVV001 is effective in the perioperative setting for reduction of bleeding during surgery.
- BIVV001 demonstrated clinical benefit in all age groups for routine prophylaxis.

The risks of BIVV001 include:

- FVIII thrombotic event development and potential hypersensitivity reactions. The risk of development of thrombosis is considered an expected AE.

The results from the phase 3 trials demonstrated a clinically meaningful benefit in reduction of ABRs for routine prophylaxis and has demonstrated hemostatic efficacy with on-demand treatment of and prevention of spontaneous or traumatic bleeding in adults and children with Hemophilia A and in the perioperative setting for reduction of bleeding during surgery. This product provides an alternative option for subjects with reduced frequency of dosing.

The most commonly reported adverse reaction included headache, arthralgia, and back pain, and were transient and mild. No neutralizing antibodies were reported following administration of BIVV001. The risks of BIVV001 include thrombosis and allergic reactions, which are expected for this class of products.

This application has provided substantial evidence of the safety and effectiveness of BIVV001 in adults and children with severe Hemophilia A. The overall benefit-risk profile favors approval of BIVV001 for use in adults and children with Hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes; On-Demand treatment and control of bleeding episodes; and Perioperative management of bleeding.

11.3 Discussion of Regulatory Options

The available data support the approval of the indication for on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis for adults and children with HA.

11.4 Recommendations on Regulatory Actions

Traditional or regular approval for the on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis indications is recommended for adults and children with HA.

11.5 Labeling Review and Recommendations

The revised package insert was reviewed, commented on, and revised by the appropriate discipline reviewers. FDA’s Advertising and Promotional Labeling Branch conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the Applicant.

11.6 Recommendations on Postmarketing Actions

No postmarketing requirement or postmarketing commitment studies are requested at this time. Review of the clinical data found no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint.

The applicant plans a post approval voluntary study to assess safety of use of BIVV001 in PUPs and there is an ongoing long-term follow-up study of clinical trial participants. For 3 years following approval, the applicant will be required to conduct enhanced pharmacovigilance for thromboembolic events (TEEs), with expedited reporting of all TEEs (regardless of seriousness) and sponsor assessment for TEEs (based on cumulative and interval safety data) in periodic safety reports.

For all other adverse events, the applicant will conduct routine pharmacovigilance.

*****Do Not Change Anything Below This Line*****